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Safety outcomes of SARS-CoV-2 vaccination in pediatric patients with a first dose reaction history or allergy to polyethylene glycol or polysorbate

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Clinical Implications

The second dose of Pfizer-BioNTech vaccine can be administered safely in children with a history of immediate and potentially allergic reactions to the first dose, as well as in children with a history of polyethylene glycol or polysorbate allergy.

Since their release in and subsequent approval for adult and pediatric patients, vaccines against SARS-CoV-2 have provided hope for ending the COVID-19 pandemic. However, reactions to mRNA vaccines early in the global vaccine rollout have hampered this effort not only by preventing the administration of a second dose but also by reducing compliance with the first dose. After clinical reports of allergic reactions were made concerning COVID-19 vaccinations, the US Centers for Disease Control and Prevention recommended that those who have an allergy to any component of the vaccine or who had an immediate allergic reaction (within 4 hours) to the first vaccine dose should not receive the second dose. Concerns were raised regarding the role of polyethylene glycol (PEG) or the chemically related polysorbate in immediate reactions given the presence of PEG 2000, an excipient used to stabilize the lipid nanoparticle in the mRNA vaccines. Since then, numerous reports have demonstrated the safety of administering the second dose of mRNA vaccine to adult patients who reacted to the first dose, as well as the safety of administering mRNA vaccine to adult patients with a history of PEG/polysorbate allergy.[1-5] Despite administration of the Pfizer-BioNTech (New York, NY) SARS-CoV-2 mRNA vaccine to patients aged 5 years and older as of October 2021, there have been no reports evaluating safety in the pediatric population. In this study, we examine the safety of the second dose of this vaccine in children with an immediate or potential allergic reaction to the first dose as well as in children with documented PEG/polysorbate allergy.

A specialized vaccine clinic evaluated children referred for suspected immediate allergic reactions to the first dose of the Pfizer-BioNTech SARS-CoV-2 mRNA vaccine or suspected PEG/polysorbate allergy. All children were evaluated from May 2021 to February 2022; their families have provided consent for the publication of clinical data. Nine children were evaluated after experiencing an allergic reaction to the first dose (average age, 13 years; range, 8-17 years). Of the nine children evaluated, only two were female (22.2%). Seven children had a history of atopy (allergic rhinitis, food allergy, asthma, and penicillin allergy) and three reported a history of anaphylaxis to food or medicine. We evaluated the symptoms reported using the 2006 National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network diagnostic criteria for anaphylaxis[6] (see Table E1 in this article's Online Repository at www.jaci-inpractice.org) as well as Brighton criteria for anaphylaxis[7] (see Table E2 in this article's Online Repository at www.jaci-inpractice.org).

Three children (33.3%) reported symptoms that met both National Institute of Allergy and Infectious Disease and Food Allergy as well as Anaphylaxis Network and Brighton criteria for anaphylaxis,[7] whereas six children (66.6%) reported symptoms that were insufficient to meet the case definition. With parental consent, eight children went on to have an in-clinic observed second-dose administration of 0.3 mL Pfizer-BioNTech SARS-CoV-2 mRNA. One child (patient 8) received the second dose at a local pharmacy owing to scheduling constraints. The vaccine was administered as a single dose without premedications. All children successfully received the second vaccination with no or minimal symptoms (Table I).

We also evaluated four children with clinical histories concerning for PEG/polysorbate allergy (Table II). Two were female, average age 16 years (range, 15-17 years). Patients A, C, and D experienced reactions to PEG-asparaginase during treatment for leukemia, whereas patient B experienced a reaction to the polysorbate component of insulin as well as reported reactions to polysorbate in imitation whipped cream and pickles. Patient C also reported an anaphylactic episode to amphotericin B that had manifested as throat tingling, trouble breathing, and oxygen desaturations. Patient B had tested positive on skin testing to polysorbate 65 and 80 several years prior, but patients A, C, and D had never been skin tested for PEG or polysorbate. All four children tolerated PEG 3350 laxative with no issues. Patient A, B, and C elected to proceed with the vaccine challenge whereas patient D elected to receive Johnson & Johnson (New Brunswick, NJ) vaccine when he turned age 18 years, 3 months after evaluation. We elected not to perform skin testing to PEG/polysorbate before the vaccine challenge based on our review of data in adult patients[2] and the recently published consensus recommendation.[8] All three children tolerated both the first and second doses of the Pfizer-BioNTech SARS-CoV-2 vaccine given as a single dose, with no symptoms.

Currently, there is limited guidance regarding how to evaluate and proceed with the second dose in children with reactions to the first mRNA vaccine dose. Because identifying anaphylaxis in children can be especially challenging, children with potential anaphylaxis should undergo careful evaluation to weigh the benefits and risks of the second dose. This study presents a cohort of children who had immediate reactions to the first Pfizer-BioNTech SARS-CoV-2 vaccine dose and received a second dose with minimal side effects. We also presented three children with a history of PEG/polysorbate allergy, who tolerated both doses of Pfizer-BioNTech SARS-

TABLE I. Patient demographics, Pfizer-BioNTech mRNA COVID-19 dose 1 reaction history, and Pfizer-BioNTech mRNA COVID-19 dose 2 challenge result

Patient ID	Age	Sex	Atopic history	Anaphylaxis (cause)	Onset after receipt, min	Signs and symptoms	Intervention	Time to symptoms resolution, h	Meet National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network criteria	Brighton score	Symptoms after second dose
1	16	F	Allergic rhinitis, food allergy (shellfish)	No	<15	Scratchy throat, tachycardia, elevated blood pressure, rash (face and torso), coughing	Diphenhydramine, lorazepam	4	Yes	2	None
2	13	M	Allergic rhinitis, asthma	No	<15	Itchy throat	No intervention	3	INS	INS	None
3	17	M	Chronic urticarial and angioedema, idiopathic anaphylaxis	Yes (idiopathic)	0.5	Itching (arm and head), cough, difficulty swallowing, vomiting, rash (face and neck), stomach pain	Diphenhydramine, epinephrine, dexamethasone, famotidine	2	Yes	2	Mild pruritus (none after booster dose)
4	15	F	No	No	10	Rash (injection site, upper chest and neck)	Diphenhydramine	1-2	INS	INS	None
5	12	M	Food allergy (peanut, sesame, egg, hazelnut), penicillin allergy	Yes (peanut)	5	Raised itchy rash (generalized)	No intervention	Several	INS	INS	None
6	8	M	No	No	10	Throat hurt, closing up, dry heaving, gagging, nausea, difficulty breathing	Epinephrine, diphenhydramine, famotidine, steroids	Several	Yes	2	None
7	10	M	Allergic rhinitis	No	120	Itchy hives	Diphenhydramine, steroids	6	INS	INS	None
8	8	M	Allergic rhinitis	No	120	Facial swelling, swelling at injection site	No intervention	2	INS	INS	None
9	10	M	Allergic rhinitis, food allergy (tree nuts)	Yes (tree nuts)	<15	Cough, throat itching	Diphenhydramine	1	INS	INS	None

INS, insufficient information to meet case definition.

TABLE II. Patient demographics and PEG/polysorbate reaction history

Patient ID	Age	Sex	Initial reaction history (year)	Atopic history	Anaphylaxis (source)	Other medical conditions	Skin testing	Date Pfizer-BioNTech vaccine given	Symptoms after administration
A	17	F	Itching, rash, lip and ear swelling within minutes after PEG asparaginase (2013)	Allergic rhinitis, oral allergy syndrome	No	Pre-B-ALL on remission (6 y)	No	August 6, 2021; second dose on August 30, 2021	None
B	16	F	Generalized pruritic rash, throat swelling, loss of consciousness after Lantus (Sanofi, Bridgewater, NJ) injection (2009)	Drug allergy (polysorbate 80)	Yes (insulin, imitation whipped cream, pickle)	Lymphopenia, neutropenia, type I diabetes status post pancreatic transplantation, hypogam-maglobulinemia	Positive to polysorbate 65 and 80	August 6, 2021; second dose on August 30, 2021	None
C	15	M	Facial swelling, hives, and blisters 60 min after PEG asparaginase (2016)	Drug allergy (PEG, trimethoprim/ sulfamethoxazole, amphotericin B)	Yes (amphotericin B)	Pre-B-ALL on remission (3.5 y)	No	September 3, 2021; second dose on September 28, 2021; booster dose on April 1, 2022	None
D	17	M	Generalized pruritic rash, hypotension, lip and periorbital swelling, nausea and vomiting 15 min after PEG asparaginase (2015)	Drug allergy (PEG)	Yes (PEG)	T-cell ALL on remission (4 y)	No	N/A; patient elected to receive Johnson & Johnson vaccine	N/A

N/A, not applicable; *PEG*, polyethylene glycol; *Pre-B-ALL*, precursor B-cell acute lymphoblastic leukemia; *T-cell ALL*, T-cell acute lymphoblastic leukemia.

CoV-2 vaccine with no issues. Contrary to the published data on an immediate vaccine reaction in adults, which report a high prevalence of reactions in females (70.9% to 86%, depending on the study[1,9]), 77.7% of the children we evaluated were male. Consistent with the adult data, most children we evaluated experienced only mild reactions to the first dose, and only three patients (37.5%) fulfilled the Brighton criteria for anaphylaxis. Our experience argues that most of these initial reactions are not supportive of an IgE-mediated mechanism. Therefore, we elect to perform these challenges without premedication, because nonsedating antihistamines may not be necessary and will not prevent true IgE-mediated anaphylaxis.

Our report adds to the growing body of literature illustrating the safety of a second dose of mRNA COVID-19 vaccines in patients with mild to moderate immediate reactions to the first dose. This study was limited by a small sample size, referral bias, and the lack of objective diagnostic measurements such as serum tryptase after the initial vaccination. However, our results reaffirm similar studies performed in adults and provide additional assurance specific to the pediatric population.

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REFERENCES

1. Chu DK, Abrams EM, Golden DBK, Blumenthal KG, Wolfson AR, Stone CA Jr, et al. Risk of second allergic reaction to SARS-CoV-2 vaccines: a systematic review and meta-analysis. JAMA Intern Med 2022;182:376-85.
2. Carpenter T, Konig J, Hochfelder J, Siegel S, Gans M. Polyethylene glycol and polysorbate testing in 12 patients before or after coronavirus disease 2019 vaccine administration. Ann Allergy Asthma Immunol 2022;128:99-101.
3. Wolfson AR, Robinson LB, Li L, McMahon AE, Cogan AS, Fu X, et al. First-dose mRNA COVID-19 vaccine allergic reactions: limited role for excipient skin testing. J Allergy Clin Immunol Pract 2021;9:3308-20.e3.
4. Mark C, Gupta S, Punnett A, Upton J, Orkin J, Atkinson A, et al. Safety of administration of BNT162b2 mRNA (Pfizer-BioNTech) COVID-19 vaccine in youths and young adults with a history of acute lymphoblastic leukemia and allergy to PEG-asparaginase. Pediatr Blood Cancer 2021;68:e29295.
5. Koo G, Anvari S, Friedman DL, Zarnegar-Lumley S, Szafron V, Kahwash BM, et al. mRNA COVID-19 vaccine safety in patients with previous immediate hypersensitivity to pegaspargase. J Allergy Clin Immunol Pract 2022;10:322-5.
6. Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006;117:391-7.
7. Ruggeberg JU, Gold MS, Bayas JM, Blum MD, Bonhoeffer J, Friedlander S, et al. Anaphylaxis: case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine 2007;25:5675-84.
8. Greenhawt M, Abrams EM, Shaker M, Chu DK, Khan D, Akin C, et al. The risk of allergic reaction to SARS-CoV-2 vaccines and recommended evaluation and management: a systematic review, meta-analysis, GRADE assessment, and international consensus approach. J Allergy Clin Immunol Pract 2021;9:3546-67.
9. Shavit R, Maoz-Segal R, Iancovici-Kidon M, Offengenden I, Haj Yahia S, Machnes Maayan D, et al. Prevalence of allergic reactions after Pfizer-BioNTech COVID-19 vaccination among adults with high allergy risk. JAMA Netw Open 2021;4:e2122255.

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TABLE E1. Anaphylaxis criteria according to 2006 National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network diagnostic criteria

Anaphylaxis is highly likely when any one of the following three criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus, or flushing; swollen lips, tongue, or uvula) and *at least one of the following:*
   a. Respiratory compromise (eg, dyspnea, wheeze or bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
   b. Reduced blood pressure or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   a. Involvement of the skin, or mucosal tissue (eg, generalized hives; itch or flush; swollen lips, tongue, or uvula)
   b. Respiratory compromise (eg, dyspnea, wheeze or bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
   c. Reduced blood pressure or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
   a. Infants and children: low systolic BP (age-specific) or >30% decrease in systolic BP*
   b. Adults: systolic BP of <90 mm Hg or >30% decrease from that person's baseline

BP, blood pressure.
*Low systolic blood pressure for children is defined as <70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 × age]) from 1 to 10 years, and <90 mm Hg from 11 to 17 years.

TABLE E2. Anaphylaxis criteria for sudden onset and rapid progression of signs and symptoms according to Brighton Collaboration case definition

Diagnostic certainty level	Criteria
1	One or more major skin AND one or more major respiratory AND/OR one or more major cardiac criteria
2	One or more major skin AND one or more minor respiratory AND/OR one or more minor cardiac criteria
	One or more major respiratory AND one or more major cardiac criteria
	One or more major respiratory AND one or more minor criteria from a different system
	One or more major cardiac AND one or more minor criteria from a different system
3	One or more minor respiratory AND one or more minor criteria from two other different systems
	One or more minor cardiac AND one or more minor criteria from two other different systems

Organ systems	Major	Minor
Skin	Generalized urticaria, generalized erythema, generalized pruritus with skin rash, generalized or localized angioedema	Generalized pruritus without skin rash, generalized prickle sensation, red and itchy eyes, localized injection site urticaria
Respiratory	Bronchospasm, stridor, upper airway swelling, respiratory distress defined by two or more of: tachypnea, use of accessory respiratory muscles, retraction, cyanosis, grunting	Persistent dry cough, hoarse voice, sensation of throat closure, difficulty breathing without wheeze or stridor, sneezing, rhinorrhea
Cardiac	Hypotension, uncompensated shock defined by three or more of: tachycardia, capillary refill time >3 s, decreased level of consciousness	Reduced peripheral circulation defined by two or more of: tachycardia, capillary refill time >3 s, decreased level of consciousness
Gastrointestinal		Diarrhea, abdominal pain, nausea, vomiting
Laboratory		S-tryptase greater than upper normal level